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Review Article

Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review

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ABSTRACT

Radiation therapy (RT) is a curative treatment option for localized prostate cancer. Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule (IDN) is an emerging treatment option that involves the prophylactic irradiation of the whole prostate while increasing RT doses to the visible prostatic tumor. Because of the lack of large multicentre trials, a systematic review was performed in an attempt to get an overview on the feasibility and efficacy of focal dose escalation to the IDN.

A bibliographic search for articles in English, which were listed in MEDLINE from 2000 to 2016 to identify publications on RT with focal directed boost to the IDN, was performed. The review was completed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Twenty-two articles describing 1,378 patients treated with RT using focal boost were identified and fulfilled the selection criteria. Intensity-modulated radiation therapy (IMRT) was used in 720 patients (52.3%), volumetric modulated arc therapy was used in 45 patients (3.3%), stereotactic body radiation therapy (SBRT) in 113 patients (8.2%), and low-dose rate and high-dose rate brachytherapy (BT) were used in 305 patients (22.1%) and 195 patients (14.1%), respectively. Use of androgen deprivation therapy varied substantially among series. Biochemical disease-free survival at 5 years was reported for a cohort of 812 (58.9%) patients. The combined median biochemical disease-free survival for this group of patients was 85% (range: 78.8–100%; 95% confidence interval: 77.1–82.7%).

The average occurrence of grade III or worse gastrointestinal and genitourinary late toxicity was, respectively, 2.5% and 3.1% for intensity-modulated RT boost, 10% and 6% for stereotactic body RT, 6% and 2% for low-dose rate BT, and 4% and 4.3% for high-dose rate BT.

This review shows encouraging results for focal dose escalation to the IDN with acceptable short- to medium-term side effects and biochemical disease control rates. However, owing to the heterogeneity of patient population and the short follow-up, the results should be interpreted with caution. Considering that the clinical endpoint in the studies was biochemical recurrence, the use and duration of androgen deprivation therapy administration should be carefully considered before driving definitive conclusions. Randomized trials with long-term follow-up are needed before this technique can be generally recommended.

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1. Introduction

Prostate cancer (PCa) is among the third most common malignancy in Europe. An estimated 417,000 PCa cases were diagnosed in Europe in 2012¹ and 1.4 million cases of PCa worldwide with

293,000 deaths in 2013². Traditionally, PCa patients have been considered for active surveillance programs or radical whole-gland therapies such as prostatectomy, external beam radiotherapy (EBRT), or brachytherapy (BT)³. In the case of EBRT, the advent of more sophisticated treatment plans yields better dose conformity to the target, allowing for dose escalation and better biochemical disease control, although not without toxicity because of the close proximity of organs at risk (OARs), particularly bladder and rectum^{4–10}.

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Abbreviations

ADT	Androgen deprivation therapy	KVCT	Kilovoltage Computed tomography
ADC	Apparent diffusion coefficient	LDR	Low dose rate
BED	Biological equivalent dose	LC	Local control
bDFS	Biological disease-free survival	MRSI	Magnetic resonance spectroscopy imaging
BT	Brachytherapy	MVCT	Megavoltage computed tomography
CTCAE	Common Terminology Criteria for Adverse Events	mpMRI	Multiparametric Magnetic Resonance Imaging
CBCT	Cone-beam Computed tomography	NCCN	National Comprehensive Cancer Network
DWI	Diffusion-weighted imaging	OAR	Organs at risk
DCE	Dynamics contrast enhancement	OS	Overall survival
DSS	Disease-specific survival	PET CT	Positron emission computed tomography
EBRT	External beam radiotherapy	PCa	Prostate cancer
ERC	Endorectal coil	PSA	Prostatic Specific Antigen
GI	Gastrointestinal	PTV	Planning Target Volume
GU	Genitourinary	PTVb	PTV boost
Gy	Gray	PTVpr	PTV prostate
GTV	Gross tumor volume	SIB	Simultaneous integrated boost
HDR	High-dose rate brachytherapy	SPECT	Single-Photon Emission Computed Tomography
IMRT	Intensity-modulated radiation therapy	SUV	Standard Uptake Value
IGRT	Image-guided radiation therapy	SBRT	Stereotactic body radiation therapy
IDN	Intraprostatic dominant nodule	T2W	T2-weighted sequence
		US	Ultrasound
		VMAT	Volumetric modulated arc therapy

Randomized data comparing different methods of dose escalation are sparse, with three randomized trials comparing EBRT plus whole prostate BT boost with EBRT alone. These trials have demonstrated improved biochemical disease-free survival (bDFS) using distinct BT boost regimens, but only the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) trial has shown significantly greater urinary side effects^{11–14}.

Importantly, studies of patterns of failure after conventionally fractionated EBRT show that the area responsible for local recurrence is the intraprostatic dominant nodule (IDN) in 90% of cases^{15–18}. The IDN is defined as the largest nodule in a multifocal disease which harbors in more than 80% of the cases the most aggressive biological behavior and therefore dictates the overall clinical prognosis of PCa¹⁹.

Retrospective studies compared the site of the primary tumor on pre- and post-EBRT magnetic resonance images (MRIs), and by using large block pathology sections of the salvage radical prostatectomy specimen as the reference gold standard, they mapped the position of the recurrent tumor within the prostate showing that the pre-EBRT intraprostatic dominant nodule visible on the MRI was responsible for the local recurrence and could be specifically targeted to receive higher doses of radiation^{15–18}.

Intraprostatic dose escalation requires advanced imaging capabilities, which can detect intraprostatic tumor deposits with acceptable sensibility and specificity. Nowadays, it is possible to identify the IDN by using multiparametric magnetic resonance image (mpMRI), which uses various T1 and T2 sequences, dynamic contrast enhancement to assess perfusion, and diffusion-weighted imaging to calculate the different diffusion capability of PCa versus normal tissue²⁰. Other imaging methods to detect the IDN such as ¹¹C-choline-positron emission computed tomography (PET/CT), ⁶⁸Ga-prostate-specific membrane antigen (PSMA) PET/CT, and newer generation ultrasound equipment are also under evaluation^{21–24}.

Furthermore, highly conformational EBRT techniques with improvement in patient positioning during treatment, such as image-guided radiation therapy (IGRT) and the use of fiducial markers to track prostate movements during a radiotherapy session, are needed for safe and effective treatment delivery^{25–27}.

Because of the lack of large multicentric trials, a systematic review was performed in an attempt to get an overview on the feasibility and efficacy of focal dose escalation to the IDN, with special attention to gastrointestinal (GI) and genitourinary (GU) toxicity as well as clinical efficacy.

2. Materials and methods

2.1. Literature search strategy

The literature review included a search in MEDLINE from 2000 to 2016, using the terms “intraprostatic” OR “intra-prostatic” OR “dominant intraprostatic lesion” OR “intraprostatic lesion” OR “gross tumor volume (GTV)” OR “simultaneous integrated boost” AND “radiation” OR “radiation therapy” OR “brachytherapy” OR “stereotactic body radiation therapy (SBRT)” OR “intensity modulated radiation therapy (IMRT)” OR “volumetric arc therapy (VMAT)” AND “prostate cancer”.

2.2. Assessment of study quality and inclusion criteria

The search results were assessed on content before inclusion into the review. The selection criteria for inclusion in the systematic review were accessible fully published articles in English, which reported the treatment outcome of PCa patients who received a boost to the IDN either by BT or EBRT. The primary endpoint was treatment-related side effects and efficacy outcome.

Articles dealing with case reports, recurrent disease, or planning studies were not included. Reports from conference proceedings were excluded. All authors participated in the design of the search strategy and inclusion criteria.

The following data were extracted from each study: pre-defined eligibility criteria, year of report, sample size, type of treatment, histology Gleason score, TNM stage, National Comprehensive Cancer Network cancer risk classification, median prostate-specific antigen, median time of follow-up, pretreatment diagnostic tools, such as imaging techniques used to localize the disease, radiotherapy technique and dose, use of androgen deprivation therapy (ADT), follow-up duration, acute

and late side effects, quality of life assessment, biochemical control, and when available disease-specific survival (DSS), overall survival (OS), and local control rate. The side effects were translated into the current classification of adverse events Common Terminology Criteria of Adverse Events version 4. Acute radiation effects are seen from day 1 through day 90, whereas late radiation effects are all adverse effects seen after 90 days from the beginning of RT.

2.3. Statistical considerations

The outcome was analyzed in terms of local control, DSS, and OS rates at 5 years. If available, estimates and 95% confidence intervals (CI), as reported in the articles, were used. To perform meta-analysis of median survival, we pooled the estimates as median survival and standard error. Ninety-five CIs were extrapolated and reported on variation, number of events, and/or median follow-up times using RStudio software, version 1.0.153.

Given the heterogeneous nature of the patient series reported, no formal attempt at a quantitation of bias or analysis of pooled results was attempted; however, qualitative appraisal of the relative strengths and weaknesses of the individual series was made,

and qualitative statements are included in the results and discussion of the articles.

3. Results

In total, twenty-two articles describing 1,378 patients were identified for data extraction. A Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of the search results is available in Fig. 1. Table 1 summarizes a patient's characteristics, type of radiotherapy delivery, and outcome.

The level of the evidence is low to medium, with no study yielding a level of evidence >2b. This suggests that the results of this review should be interpreted with caution. Of particular importance is the fact that we were unable to retrieve the exact definition of IDN used in each study.

The median follow-up for the 1,378 patients was 36 months (range 3–86 months).

3.1. Patient's characteristics

The analyzed literature^{28–49} included 323 (23%) patients with National Comprehensive Cancer Network low-risk disease, 509 (37%) patients with intermediate-risk disease, and 517 (38%)

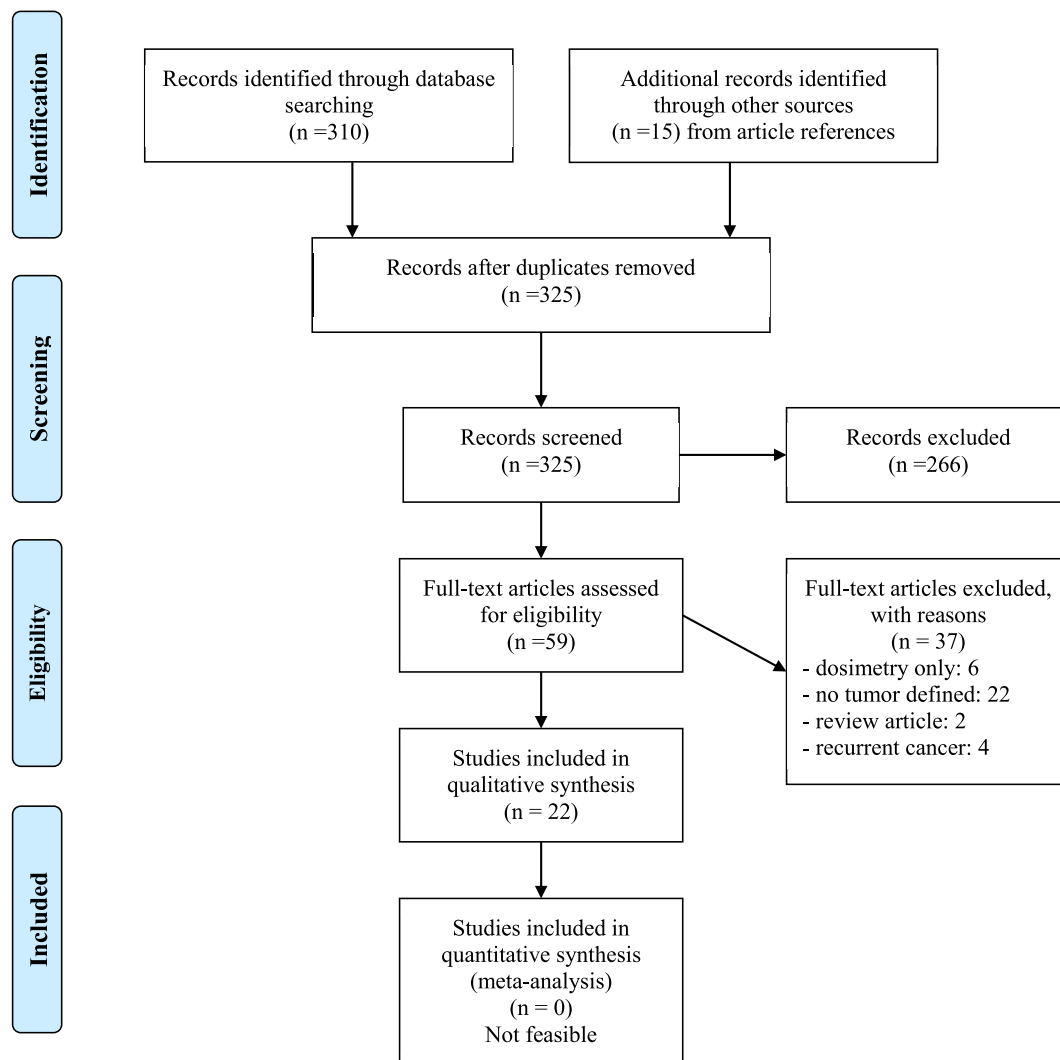


Fig. 1. Diagram showing the results from the literature search using PubMed and from the selection of articles, resulting in the withholding of 22 articles reporting on results of treatment using focal dose irradiation to the intraprostatic dominant nodule.

Table 1
Literature summary of prostate irradiation with intraprostatic directed boost

Author	N	IDN identification modality	Treatment technique	NCCN	Median PSA ($\mu\text{g/L}$)	Median follow-up time	Volume delineation and margins	Boost technique	Dose (Gy/fr)	ADT	5-year bDFS (phoenix)	Survival (DSS, OS)
Zelevsky et al ²⁸	4	1,5T ERC MRSI (elevated choline + elevated creatine-to-citrate ratio)	LDR B (I125)	LR (2) IR (2) HR (0)	4.5	NR	PTVb = GTV PTVpr = prostate	LDR B (I125)	PTVb = 150% of PTVpr PTVpr = 100–145 Gy	No	NR	NR
DiBiase et al ²⁹	15	1,5T ERC MRSI (elevated choline + elevated creatine-to-citrate ratio)	LDR B (I125)	LR (15) IR (0) HR (0)	7.1	NR	PTVb = GTV PTVpr = prostate + 2 mm	LDR B (I125)	PTVb = 188 Gy PTVpr = 145 Gy	No	NR	NR
De Meerleer et al ³⁰	15	1,5T ERC MRI (T2W) + biopsy	IMRT (3 field, Step and Shoot)	LR (2) IR (8) HR (5)	10.2	NR	PTVb = GTV PTVpr = (prostate + SV) + 7–10 mm	IMRT	PTVb = 80 Gy/37 PTVpr = 74 Gy/37	Yes (73%) neoadj + adj (6–36 mo)	NR	NR
Singh et al ³¹	3	3T ERC MRI (T2W + DCE + DWI) + biopsy	IMRT	NR	NR	3–18	PTVb = GTV + 3 mm PTVpr = prostate + 7 mm		PTVb = 94.5 Gy/42 PTVpr = 75.6 Gy/ 42	No	NR	NR
Fonteyne et al ³²	230	1,5T ERC MRI (T2W + T1W) or MRSI	IMRT (3 field, Step and Shoot)	LR (17) IR (97) HR (116)	11.2	NR	PTVb = GTV + 4 mm PTVpr = (prostate \pm SV) + 4 mm	IMRT	PTVb = 80 Gy/39 PTVpr = 78 Gy/39	No	NR	NR
Ares et al ³³	77	ERC MRI (T2W + DCE) + biopsy	3DCRT + HDR B (Ir192)	LR (6) IR (25) HR (46)	NR	41.2	PTVb = boost prostate volume PTVpr = prostate + VS PLN	HDR B (Ir192)	PTVb = 85.6–99.2 Gy PTVpr = 64 Gy/32	Yes (>80%) neoadj/adj (18–24 mo)	78.8%	90% 5-year DSS
Miralbell et al ³⁴	50	ERC MRI (T2W + DCE) + biopsy	3DCRT/IMRT (Step and shoot, sliding window and VMAT)	LR (5) IR (12) HR (33)	NR	NR	PTVb = GTV + 3 mm PTVpr = prostate + SV PLN	SBRT	PTVb = 80–99 Gy PTVpr = 64 Gy/32	Yes (66%) neoadj + adj (6–30 mo)	98%	100% 5-year DSS
Schick et al ³⁵	77	ERC MRI (T2W + DCE) + biopsy	3DCRT + HDR B (Ir192)	LR (7) IR (9) HR (61)	NR	62–67	PTVb = hemi prostate PTVpr = prostate + vs PLN	HDR B (Ir192)	PTVb = 88–104 Gy PTVpr = 64.4 Gy/ 32	Yes (81%) neoadj + adj (18–24 mo)	70.5–79.7%	NR
Ellis et al ^{36,37}	239	111In-Capromab SPECT Imaging	LDR prostate + 3DCRT in 37%	LR (116) IR (94) HR (29)	7.6	84	PTVb = GTV + 5 mm PTVpr = prostate + 2 –5 mm \pm PLN	LDR prostate (Pd103 or I125)	PTVb = 150% of PTVpr PTVpr = 108–144 Gy (I125) PTVpr = 100–125 Gy (Pd103)	Yes (21%) neoadj	84.6%	97.7% 10-year DSS 84.8% 10-year OS
Wong et al ³⁸	71	111In-Capromab SPECT Imaging	IMRT	LR (31) IR (30) HR (10)	6.1	66	PTVb = GTV PTVpr = prostate + SV (when involved) + 6 mm	IMRT	PTVb = 82 Gy (SIB) PTVpr = 75.6 Gy/ 42	Yes (24%) adj (6–12 mo)	94%	93% 5-year OS
Pinkawa et al ³⁹	66	18F-Fluorocholine PET CT	IMRT	LR (23) IR (21) HR (22)	14	19	PTVb = GTV + 3–4 mm PTVpr = prostate + SV + 4–8 mm	IMRT	PTVb = 80 Gy (SIB) PTVpr = 76 Gy/38	Yes (16%) (NR)	NR	NR
Ippolito et al ⁴⁰	40	1,5T ERC MRI + biopsy	IMRT	LR (4) IR (17) HR (19)	7	19	PTVb = (GTV + 5 mm) + 1 cm PTVpr = prostate + SV + 1 cm	IMRT	PTVb = 80 Gy (SIB) PTVpr = 72 Gy/40	Yes (100%) neoadj + adj(24 mo)	100%	NR
Myers et al ⁴¹	26	TRUS	IMRT + HDR B (Ir192)	LR (7) IR (19) HR (0)	6.1	53	PTVb = peripheral zone PTVpr = (prostate + 1.5 cm + VS + 5 mm) + 5 mm PLN	HDR B (Ir192)	PTVb = 9 Gy + 63 Gy/28 PTVpr = 6Gy + 63 Gy/28	Yes (73%) neoadj + adj(4 mo)	100%	NR
Aluwini et al ⁴²	50	1.5 T MRI (T1W + T2W)	SBRT (Cyberknife)	LR (30) IR (20) HR (0)	8.2	23	PTVb = GTV PTVpr = prostate + 3 mm	SBRT (Cyberknife)	PTVb = 44 Gy (SIB) PTVpr = 38 Gy/4, daily	No	100% 2-year bDFS	NR

Schild et al ⁴³	78	1.5 T MRI (T2W + DCE + DWI)	IMRT (sliding window and VMAT)	LR (18) IR (43) HR (17)	6.7	36	PTVb = GTV PTVpr = prostate + 3 mm	IMRT (sliding window and VMAT)	PTVb = 81–83 Gy (SIB) PTVpr = 77.4 Gy/43	Yes (41%) adj(6–30 mo)	92% 3-year bDFS	95% 3-year OS
Gomez-Iturriaga et al ⁴⁴	15	1.5 T MRI (T2W + DCE + DWI)	IMRT + HDR B (Ir192)	LR (0) IR and HR: not specified	9	18	PTVb = GTV PTVpr = prostate	HDR B (Ir192)	PTVb = 18.75 Gy + 37.5 Gy/15 PTVpr = 15 Gy + 37.5 Gy/15	No	NR	NR
King et al ⁴⁵	47	MRSI (elevated choline + elevated creatine-to-citrate ratio)	LDR (I125 or Pd103) + IMRT PLN for 1 patient	LR (35) IR (12) HR (0)	5.1	86.4	PTVb = GTV PTVpr = prostate PLN	LDR (I125 or Pd103)	PTVb = 150% of PTVpr PTVpr = 144 Gy (I125) or 140 Gy (Pd103)	Yes (17%) neoadj	98% 10-year bDFS	84% 10-year OS
Sundahl et al ⁴⁶	225	1.5T ERC MRI or 3T MRI (T1W + T2W)	IMRT	LR (5) IR (97) HR (123)	NR	72	PTVb = GTV PTVpr = prostate ± SV + 7 mm	IMRT	PTV1 = 82 Gy (SIB) PTV2 = 78 Gy/38	No	84% 6-year bDFS	NR
Kotecha et al ⁴⁷	24	MRI (no specification)	SBRT (Cyberknife)	LR (0) IR (11) HR (13)	NR	25	PTVb = GTV PTVpr = prostate + SV + 3 mm (0 mm posteriorly)	SBRT (Cyberknife)	PTVb = 50 Gy (SIB) PTVpr = 36.25 Gy/5	Yes (67%) Adj(4–30 mo)	95.8% 2-year bDFS	NR
Uzan et al ⁴⁸	11	MRI (T2W + DCE + DWI) + biopsy	IMRT (VMAT)	NR	15.9	36	PTVb = GTV + 5 mm PTVpr 1 = prostate + SV + 9 mm PTVpr 2 = prostate and base of SV + 5 mm	IMRT (VMAT)	PTVb = 85–105 Gy (SIB) PTVpr1 = 64 Gy/37 PTVpr2 = 74 Gy/37	Yes (100%) neoadj + adj (6–36 mo)	NR	NR
Garibaldi et al ⁴⁹	15	1.5 ERC MRI (T2W + DWI + DCE)	IMRT (VMAT)	LR (0) IR (14) HR (1)	6.5	16	PTVb = GTV + 6 mm PTVpr 1 = prostate + 7 mm (5 mm posteriorly) PTVpr 2 = SV + 5–7 mm	IMRT (VMAT)	PTVb = 83.2 Gy (SIB) PTVpr1 = 75.2 Gy/32 PTVpr2 = 67.2 Gy/32	Yes (80%) neoadj + adj (6–24 mo)	100%	NR

3DCRT, 3-D conformational radiation therapy; ADT, androgen deprivation therapy; Adj, adjuvant ADT; bDFS, biochemical disease-free survival; CTCAE v2, Common Terminology Criteria of Adverse Events version 2, CTCAE v4, Common Terminology Criteria of Adverse Events version 4; DCE, dynamic contrast enhancement; DSS, disease-specific survival; EORTC, European Organization for Research and Treatment for Cancer; DWI, diffusion-weighted imaging; EPIC, Expanded Prostate Cancer Index Composite questionnaire; ERC, endorectal coil; Fr, fraction; GI, gastrointestinal; GTV, Gross tumor volume (=dominant intraprostatic lesion); GU, genitourinary; Gy, gray; HDR, high-dose rate brachytherapy; HR, high risk; IDN, intraprostatic dominant nodule; IMRT, intensity-modulated radiation therapy; IR, intermediate risk; LDR B, low-dose rate brachytherapy; LR, low risk; MRI, magnetic resonance imaging; mpMRI, multiparametric MRI [T2 weighed + dynamic contrast enhancement (DCE) + diffusion-weighted imaging (DWI)]; MRSI, magnetic resonance spectroscopic imaging; NCCN, National Comprehensive Cancer Network; Neoadj, neoadjuvant ADT; NR, not reported; OS, overall survival; PET CT, positron emission tomography–computed tomography; PLN, pelvic lymph nodes irradiation; PLND, pelvic lymph nodes dissection; PSA, prostate-specific antigen; PTV, planning target volume; PTVb, boost; PTVpr, whole prostate; SBRT, stereotactic body radiation therapy; SPECT, single-photon emission computed tomography; SV, seminal vesicles; TRUS, transrectal ultrasound; VMAT, volumetric modulated arc therapy.

patients with high-risk disease. Three studies did not specify the risk group (29 patients, 2.1%).

3.2. Disease localization

The spatial location of the tumor within the prostate is essential for dose escalation of radiotherapy treatment. There is no accepted standard for disease localization for the purpose of delivering boost therapy.

In 976 patients (70.8%; $n = 17$ studies), an MRI was used to identify the IDN. From those series, five (488 patients, 35.4%) used magnetic resonance spectroscopy imaging (Choline/creatine-to-citrate ratios >1.4 – 2) to define the tumor^{28,29,32,33,45}, three series (116 patients, 8.4%) used 3T MRI, and nine series (438 patients, 31.7%) used mpMRI (with sequences T2W + dynamic contrast enhancement + diffusion-weighted imaging)^{31,33–35,43,44,46,49,48}, of which two studies used open MRI^{33,35}.

Six hundred ninety-eight patients (71.5%) ($n = 15$ studies) of 976 underwent 1.5 T magnetic resonance imaging with an endorectal coil to identify the IDN. Two series (162 patients, 16.6%) used MRI without an endorectal coil^{42,46}.

One study with 66 patients (4.8%) used 18-Fluorocholine PET/CT imaging³⁹ [with a gross tumor volume (GTV) = standard uptake value (SUV) $> 2 \times$ background]. Three studies (310 patients, 22.5%) used ¹¹¹In-Capromab single-photon emission computed tomography^{36–38} (with a GTV = SUV $3 \times$ muscle SUV) for tumor localization.

Only one study (26 patients, 1.9%) used transrectal ultrasound (TRUS) to identify the tumor during the HDR BT treatment⁴¹. In 476 patients (49.9%) treated with BT, the procedure was delivered under US ($n = 7$ studies, 3 studies with transrectal and 4 studies with transabdominal US).

The mean percentage of IDN identified and irradiated was 80.4% (range 28–100%).

3.3. Radiotherapy planning

MRIs, PET CT, or single-photon emission computed tomography images used to identify the IDN were transferred to the radiotherapy planning computed tomography images through automatic rigid image registration (1079 patients, 78.3%, $n = 16$ studies)^{31–35,38–40,42–49} or manual transfer (269 patients, 19.5%, $n = 4$ studies)^{29,30,36,37}. The visible tumor was considered as GTV by all the studies. Most series defined the planning target volume (PTV) as the GTV with an extension of 3- to 4-mm margins, excluding OARs. None of the studies used a margin for clinical target volume around the GTV, and thus, the boost PTV comprised the tumor with a margin of 1–3 mm. The prostate PTV definition varied among series. It most commonly included prostate + seminal vesicles when they were involved and an isotropic extension of 3–7 mm.

Deformable registration was used in only one study (4 patients, 0.3%)²⁸. Fiducial markers were used for tracking intrafraction and interfraction tumor movement in five studies (168 patients, 12.2%)^{31,41–43,48}.

In the case of BT, only one study (26 patients, 1.9%)⁴¹ used TRUS to define the IDN.

3.4. Protection of healthy tissue

OARs contouring guidelines varied among studies, and most of the studies considered rectum, bladder, and bowel as critical organs to be preserved from high doses of radiation. Efforts to spare the urethra were made in 14 studies (830 patients, 60.2%).

A total of 127 patients (9.2%) in two studies were treated with a rectal balloon to reduce internal organ immobilization^{33,34}.

3.5. Radiotherapy delivery

A total of 878 patients (63.7%) were treated with EBRT with focal boost using

1. IMRT (720 patients, 52.3%, $n = 8$ studies)
2. VMAT (34 patients, 2.5%, $n = 3$ studies)
3. SBRT (124 patients, 8.9%, $n = 3$ studies). Fig. 2

A total of 500 patients (36.3%) were treated with BT with focal boost using

4. Low-dose rate brachytherapy (LDR BT) (305 patients, 22.1%, $n = 4$ studies)
5. HDR BT (195 patients, 14.1%, $n = 4$ studies).

3.6. External beam radiation therapy setup monitoring

Online corrections through IGRT to minimize patients' setup uncertainty were used at different frequencies in 941 patients (68.2%; $n = 15$ studies). Fifteen patients of 941 (1.5%) were monitored with daily megavoltage computed tomography ($n = 1$ study), 236 patients (25%) were monitored with daily cone-beam CT ($n = 2$), 152 patients (16.1%) were monitored with kilovoltage computed tomography ($n = 3$), 18 patients (1.9%) with daily portal images ($n = 1$), and 50 patients (5.3%) with daily monitoring of infrared skin-reflecting markers.

Fiducial markers were used for tracking intrafraction and interfraction tumor movement in five studies (168 patients, 12.2%)^{31,41–43,48}.

3.7. Target doses and organs at risk dose constraints

For the purpose of this review, all doses were converted to EQD2 (equivalent dose in 2-Gy fractions) with $\alpha/\beta = 1.5$ Gy for prostate^{50,51} and $\alpha/\beta = 3$ Gy for OARs.

Most of the studies using EBRT prescribed the radiation dose to isocenter to cover homogeneously 98–100% of the prostate PTV. For IMRT series, the mean doses delivered to the PTV boost (PTVb) were 89 Gy (range 80–130 Gy), and the mean dose to the prostate PTV was 74.7 Gy (range 67.9–82.7 Gy). The average differential dose [PTVb–PTV prostate (PTVpr)] was 14.8 Gy (range 3.2–29.9 Gy).

For the VMAT series, the mean dose to the PTVb and PTVpr were 104 Gy (range 92.2–130 Gy) and 78 Gy (range 74–82.7 Gy), respectively. The average differential dose was 26 Gy (range 17–35 Gy).

For the SBRT series, the PTVb and PTVpr mean doses were 136.4 Gy (range 89.7–164.3 Gy) and 91.4 Gy (range 64–119.4 Gy), respectively. The average differential dose was 45 Gy (range 25.7–73.5 Gy). The most common EBRT rectal dose constraint was $V70 < 15$ –30% with rectal Dmax of 76–80 Gy. Bladder dose constraint was $V70 < 15$ –30% and Dmax of 80 Gy. The urethra Dmax was ≤ 74 –113 Gy when it was possible to spare, depending on the modality used.

For the BT series, I125 or Pd103 LDR was most commonly used with a mean PTVb and PTVpr dose of 177.5 Gy (range 150–217 Gy) and 123 Gy (range 100–145 Gy), respectively. The average differential dose was 61.8 Gy (range 43–72 Gy). The urethra Dmax was < 85 –150% of the PTVb dose and rectal Dmax was $< 120\%$ of the PTVb.

For HDR BT the mean dose for PTVb and PTVpr were 106.3 Gy (range 89.7–151.3 Gy) and 80.5 Gy (range 64–113.6 Gy). The average differential dose was 31.7 Gy (range 25.7–43.4 Gy).

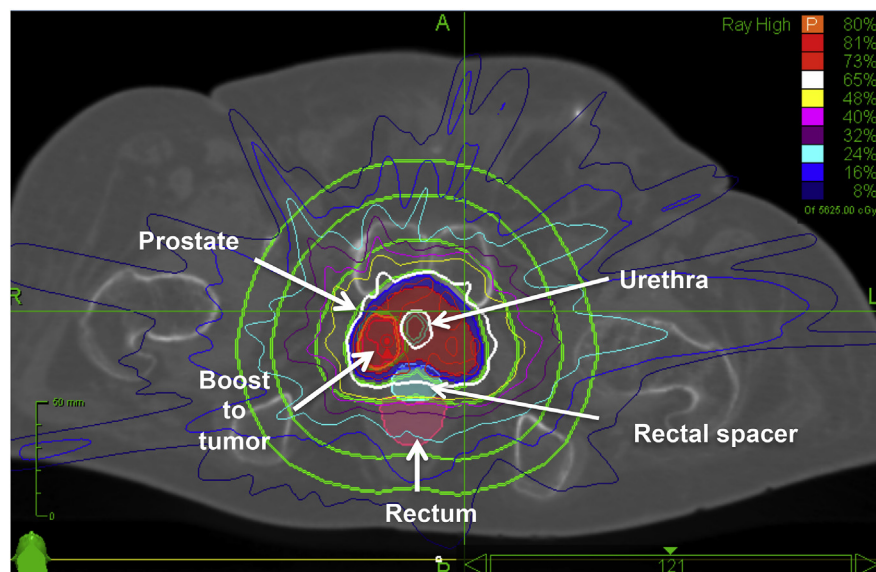


Fig. 2. Stereotactic body radiation therapy plan using Cyberknife. The patient is treated in the context of the HYPORP phase I/II trial (NCT02254746) that the authors of this review perform at the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. The tumor is located in the right posterior prostate lobule. Fiducial markers are placed in the prostate for robotic-assisted tracking purposes. A rectal balloon spares the rectum from high doses of radiation. The prostate is treated with 36.25 Gy in five fractions of 7.25 Gy with a boost of 50 Gy to the intraprostatic dominant nodule. Red lines represent prescription isodose (80%).

A total of 153 patients (11.1%) in five studies received pelvic lymph node irradiation with a total dose of 50.4 Gy in 28 fractions^{33–35,41,45}.

3.8. Androgen deprivation therapy

ADT varied among series.

A total of 384 patients (27.8%) in 15 studies were treated with ADT^{30,33–41,43,45,47–49,52}. Three hundred twenty-three patients of 384 (84%) in 12 studies were treated with adjuvant ADT. Neo-adjuvant ADT was used in 300 patients (78%; $n = 10$ studies). Usually, EBRT started 1–3 months after the first day of hormonal blockage. The ADT lasted 6 months for intermediate-risk patients and 2–3 years for high-risk patients.

3.9. Disease outcome

The median follow-up for the 1,378 patients was 36 months (range 3–86 months).

bDFS at 5 years was reported for a cohort of 812 (58.9%) patients in eight studies^{33–35,37,38,41,45,46}. The median bDFS for these series was 85% (range 78.8–100%; 95% CI: 77.1–82.7%). Fig. 3.

Other survival outcomes included 5- to 10-year OS which was reported for 357 patients (25.9%) and had a median of 85% (range from 84% to 93%). DSS was also studied for 366 patients (26.5%) with a median of 97.7% at 5 years (range 90–100%).

3.10. Side effects

According to the RT technique, the median grade 3 or more acute and late GI toxicity were 5% and 2.5% for IMRT boost, respectively; 2% and 10% for SBRT, respectively; 0% and 6% (range 1–11%) for LDR BT, respectively; and 0% and 4% for HDR BT, respectively.

Grade 3 or more acute and late GU toxicity were 4.4% (range 1–7%) and 3.1% (range 2–5%) for IMRT boost, respectively; 6% (range 4–8%) and 6% for SBRT, respectively; 0% and 2% for LDR BT, respectively; and 2.8% and 4.7% for HDR BT, respectively. Fig. 4.

Grade 4 late GI toxicities was reported in four studies with a median of 2% (range 1–4%). One study reported a 1% GU late grade 4 toxicity^{35–37}. In these reports, three patients had rectovesical fistulae, and one had hematuria. The studies reporting late grade 4 toxicity used the following technology: IMRT ($n = 1$ study), LDR BT ($n = 2$ studies), and HDR BT ($n = 1$ study).

The acute and late grade 1–2 GI toxicity were 20.1% (range 6.6–45%) and 6.2% (range 0–21%) for IMRT boost, respectively; 6.7% (range 0–12%) and 7% (range 3–10%) for SBRT, respectively; 21.3% (range 0–60%) and 11.5% (range 2–21%) for LDR BT, respectively; and 6.6% (range 2.6–13.4%) and 6.14% (range 0–11.5%) for HDR BT, respectively.

The mean acute and late grade 1–2 GU toxicity were 39.2% (range 13.3–66%) and 18.8% (range 5–39%) for IMRT boost, respectively; 33% (range 15–46%) and 10% (range 8–12%) for SBRT, respectively; 28.5% (range 4–53%) and 13% for LDR BT, respectively; and 9.6% (range 3–20%) and 8.35% (range 6.7–11.5%) for HDR BT, respectively Supplementary Fig. 5.

4. Discussion

Multiple studies have confirmed the importance of delivering sufficiently high doses of radiotherapy to the prostate to cure patients⁴. First-class radiation technology and appropriate imaging technology are absolute prerequisites to safely deliver higher focal doses to prostate tumor/s.

In our review of the literature, we were able to identify 1,378 patients treated with whole prostate irradiation and dose escalation to the IDN.

We showed that the adoption of new technologies is strongly associated with an increase in the radiation doses delivered to the IDN. The average differential doses between the prostate and the boost increased with more complex technologies. Patients treated with IMRT had modest differential doses between PTVpr and PTVb of only 14.8 Gy compared with 25 and 45 Gy for those patients treated with VMAT and SBRT, respectively.

This systematic review highlights that when dose escalation to the dominant nodule is delivered either with IMRT, VMAT,

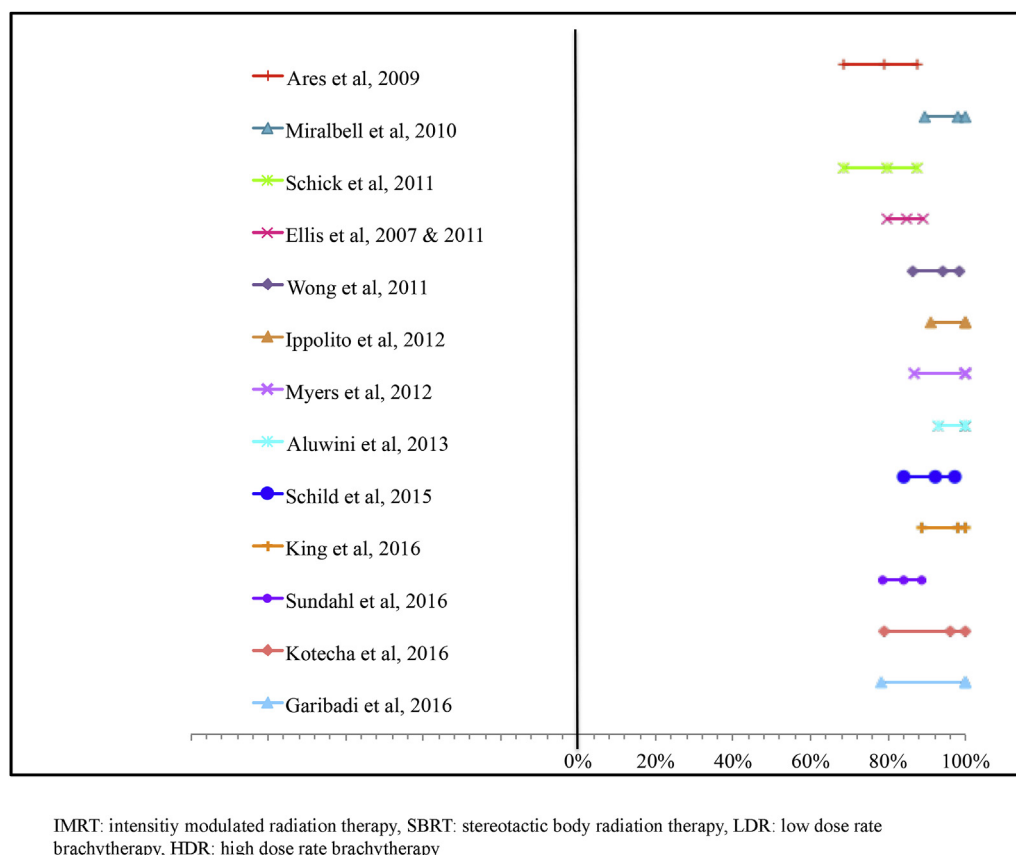


Fig. 3. Forest plots presenting the 5-year biochemical disease-free survival with their calculated 95% confidence interval from the included articles where this could be retrieved.

SBRT, or BT, the functional and disease control outcomes are encouraging. We showed that at a short-to-medium follow-up time, the grade 3 or more GU and GI late toxicity were in the order of 3% to 11%. We recognize that these rates may underestimate the true toxicity rates that may develop with longer follow-up. Nevertheless, Fig. 4 and Supplementary Fig. 5 illustrate that the toxicities for the different modalities compare favorably with those observed with other radiation modalities depicted in Supplementary Table 2.

This is in striking contrast to studies of whole prostate dose escalation using SBRT delivered in five fractions of 45, 47.5, and 50 Gy which showed 10.6% late grade 3 or more GI toxicity at the highest dose level. In that study, late grade 3 or more rectal toxicity was strongly correlated with the volume of rectal wall receiving 50 Gy > 3 cm³ ($P < 0.0001$) and treatment of >35% circumference of rectal wall to 39 Gy ($P = 0.003$)⁵³. This highlights the need for limiting the dose escalation to a defined area of the prostate while new methods are needed for minimizing rectal toxicity. The use of a rectal spacer has been proven in randomized trials to be an effective method to reduce GI side effects and maintain the patient's quality of life⁵⁴. These methods should be implemented in future trials of prostate dose escalation.

It is important to note that in our review, the series with the highest boost differentials included 66 patients with reported late grade 3 or greater toxicities that ranged from 0% to 10% including one patient with fistula formation^{34–37}. This series used large (hemi prostate or bilateral prostate GTV) volumes with relatively high boost doses. More importantly, these series did not make any attempt to protect the rectum with the use of a rectal spacer or balloons to separate, as much as possible, the rectum from high radiation doses.

The side effects reported in our systemic review are not necessarily different compared with other forms of PCa treatment. Table 1, Fig. 3, Supplementary Table 2.

In general, GU toxicity has always remained a challenge for new radiation technology. For instance, patients treated with IMRT or 3DCRT in the Radiation Therapy Oncology Group protocol¹⁴ had 40% incidence of GU grade 3 late toxicity. Ma et al⁵⁵ recently published a prospective study where 1,198 patients with different urological complications were admitted in an emergency service. Seventy-seven percentage of the admissions were elective and 23% were emergency. Thirty-three patients of 1,198 had grade 3 or more complications related to previous exposure to radiotherapy, representing the 1.4% and 7.2% of the elective and emergency admissions, respectively. From these 33 patients, 15 patients had PCa, and four of them were initially treated with radical prostatectomy followed by EBRT. The main mode of RT was EBRT (delivered in a median of 34.5 fractions of 2 Gy, median dose 70 Gy). Importantly, the median time from EBRT treatment to admission was 4 years (range 1–9 years). This study highlights that although radiotherapy complications represented a small proportion of the emergency admissions, the gravity of the side effects trigger a surgical intervention or invasive management many years after the primary treatment. In line with this observation, in the phase III randomized ASCENDE-RT trial, the 5-year cumulative incidence of grade 3 or more GU events was 18.4% for LDR-BT versus 5.2% for standard 78 Gy IMRT ($P < 0.001$). Along the same lines, the 5-year cumulative incidence of grade 3 GI events was 8.1% for LDR-BT versus 3.2% for standard EBRT ($P = 0.124$).¹⁴ Protocols using protons or SBRT have demonstrated very low incidence of severe side effects although these comparisons of technology need to be corroborated in a head-to-head clinical trial.

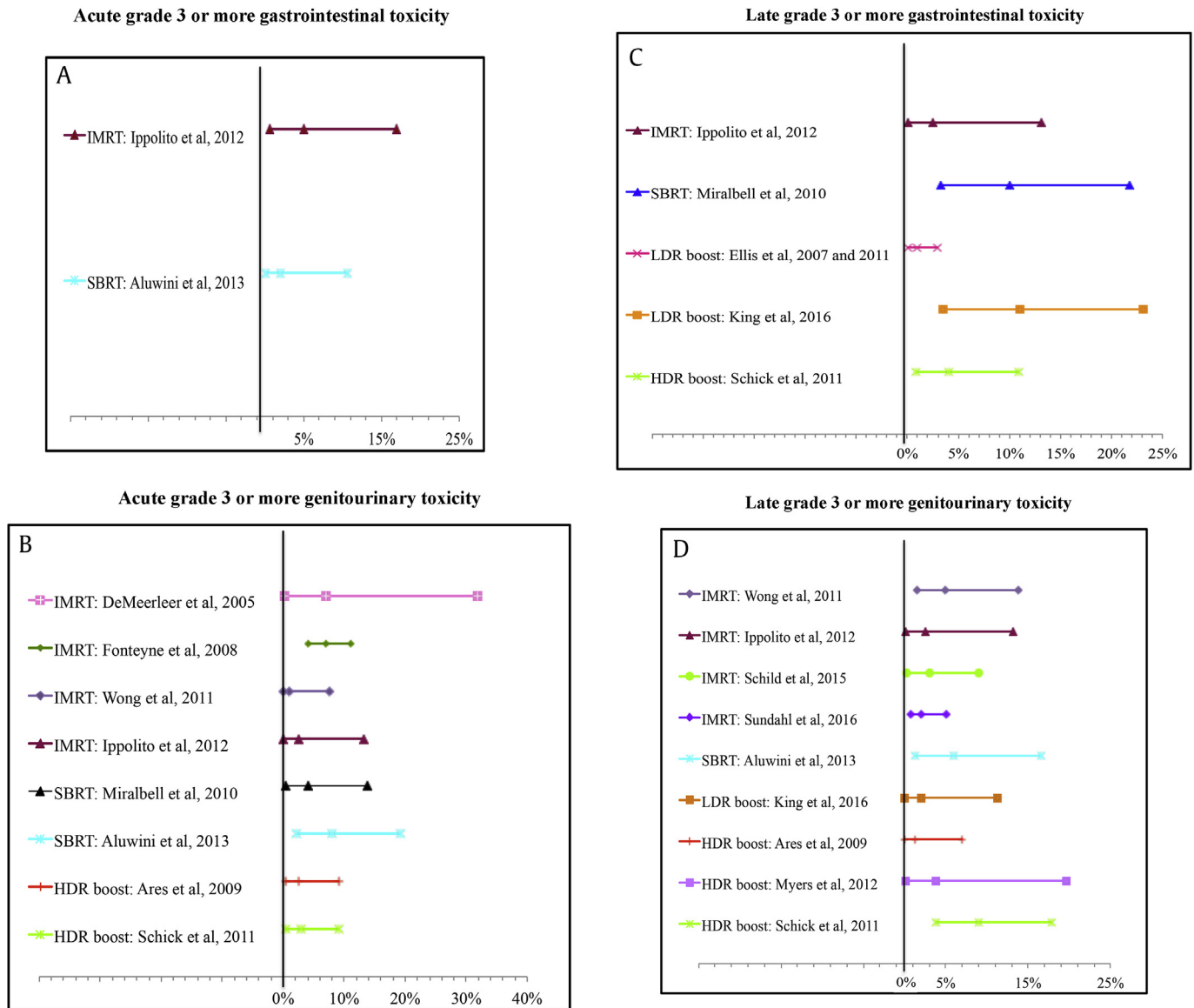


Fig. 4. Forest plots presenting the grade 3 or more: acute gastrointestinal (A), acute genitourinary toxicity (B), late gastrointestinal (C), and late genitourinary toxicity (D) with their calculated 95% confidence interval from the included articles where this could be retrieved.

IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy; LDR, low-dose rate brachytherapy; HDR, high-dose rate brachytherapy.

Furthermore, it is widely believed that younger PCa patients are at greater risk of toxicity after radiotherapy; therefore, large randomized trials with long-term follow-up are required to see if new radiotherapy treatments help all patients with PCa.

Our systematic review demonstrates that biochemical control is achieved in 80–100% of cases when using directed dose escalation to the IDN. The summary outcomes presented in Table 1 and Fig. 3 compared well with the historical EBRT trials and other radiation series that used different modalities and have mature follow-up. Supplementary Table 2. However, despite these encouraging results and because of the variability of patient selection, use of ADT, and length of follow-up, it is difficult to preclude definitive statements regarding efficacy of the boost techniques.

King et al⁵⁶ demonstrated the favorable therapeutic ratio obtained in a consortium of patients from phase 2 whole prostate SBRT trials who were treated between 2003 and 2011 at eight

institutions. Five-year bDFS was achieved in 95, 84, and 81% of low-, intermediate-, and high-risk patients, respectively. The use of ADT and SBRT dose did not significantly affect bDFS even after stratifying by risk group. In a recent randomized trial that included 218 intermediate- to high-risk patients and that compared EBRT + BT boost (35.75 Gy in 13 fractions followed by a HDR-BT boost of 2×8.5 Gy in 24 h) versus EBRT (55 Gy in 20 fractions), there was a significant improvement in bDFS for EBRT + HDR-BT, with a median time to relapse of 116 months compared with 74 months for EBRT alone. The 5-, 7-, and 10-year bDFS estimates were 75%, 66%, and 46% for EBRT + HDR-BT boost compared with 61%, 48%, and 39% for EBRT alone (log rank $P = 0.04$), with no significant difference in side effects. In univariate and multivariate analysis, treatment arm and risk category were significant covariates for risk of biochemical relapse as was the use of ADT¹³.

Although our systematic review exhaustively investigated different aspects of patient selection, treatment delivery, and

outcome, there were areas that could not be evaluated and therefore constitute the limitations of this study. Nevertheless, it is pertinent to discuss these limitations and controversies in an attempt to improve future trial designs. Owing to the heterogeneity of patient selection, we were unable to determine the disease outcome by risk category. The EBRT series reported were comprised of primarily intermediate- to high-risk patients; the BT series included a higher proportion of low-risk patients. It should be thus highlighted that according to the natural history of PCa, dose escalation RT should be delivered to patients who are likely to benefit from active treatment, whereas men with clinically insignificant disease should be monitored carefully by active surveillance.

Specifically, the patients targeted with whole-gland dose irradiation and focal boost should be those with multifocal disease but a clinically significant nodule localized in one area of the prostate. This dominant nodule has been reported to be responsible for local recurrences and drives the natural history of the disease^{15–18,57,58}. In our systematic review, most of the studies used pretreatment MRI as criteria to define the IDN. Although one investigator⁴¹ in our review used TRUS, this method has been reported to be inaccurate for localizing disease,⁵⁹ and less information is available on PET/CT imaging²². In general, it is accepted that imaging in the form of a high-quality mpMRI reported by expert radiologists may have the performance required to localize significant areas of PCa. Evidence is building to show that an area deemed negative on mpMRI stands a 95% probability of having no clinically significant disease as defined by the presence of any Gleason pattern 4 and/or a lesion volume of ≥ 0.5 ml^{60,61}. Nevertheless, the diagnostic accuracy of mpMRI to detect IDNs is still a matter of debate and cannot be a solid prerequisite to rationally target these lesions with higher doses of radiation. Therefore, mpMRI should be accompanied by US fusion-targeted biopsy sampling that will allow the detection and biological characterization of the IDN.⁶² Furthermore, the use of MRI-based radiotherapy planning is still a matter of debate because of the interobserver variability in GTV contouring and concerns about geometric distortions from the MRI system and the patient to be imaged^{63,64}.

In our review, we assumed that most investigators aimed at treating all known visible areas of cancer. We could not obtain information regarding lesions that could deliberately be excluded from the boost area and thus could have been underdosed. This could be the situation in the case where multiple nodules exist in close contact with organs at risk, and thus, the investigator may deliberately decide not to boost them to avoid overdosage of healthy tissue. Indeed, nowadays, it is difficult to ascertain which of the prostate nodules has clinical significance and is likely to have an impact on life expectancy. It is difficult to ascertain if the EBRT dose delivered to the whole gland is sufficient^{65–67} to eliminate these tumors. Thus, this area will require further clinical studies to be able to define the biology of prostate tumors that require dose escalation treatment and the radiotherapy dose constraints for the OARs that may limit the delivery of radiation to several dominant nodules. Clinicians have abandoned the use of posttreatment prostate biopsies, but this may constitute the only method to increase our knowledge on the biology of the IDN. As clinicians, we should aim at a better stratification of patients far beyond the current use of clinical prognostic factors. This will allow offering our patients an individualized cancer treatment with local therapy alone or combination with systemic therapy. To explore this, the Radiation Therapy Oncology Group has performed immunohistochemical markers on tissue samples from patients treated in phase III radiotherapy trials⁶⁸ (with and without ADT). Immunohistochemical-based assessment of protein cell surface expression for p53, p16, Cox-2, PKA, Ki-67, MDM2, BCL2, and Bax were analyzed. Both

Ki-67 and bcl2/bax were independently related to early relapse. Another approach is to study the somatic tumor genetics on tissue derived from pretreatment and posttreatment biopsies. The laboratory of Bristow et al has identified c-MYC, NKX3.1, PTEN, STAR, and HSD17B2 as adverse prognostic factors after EBRT^{69–71}. Novel gene signatures reflective of the underlying biology of PCa progression are also being developed in biopsy material and radical prostatectomy specimens (i.e., Myriad Genetics Prolaris Score, Genome Health OncotypeDx, Genomic Prostate Score, GenomeDx Biosciences Decipher, Nuclear Factor kappa B (NF- κ B)-activated recurrence predictor 21⁷²). Careful monitoring of tumor vascularization, hypoxia, DNA damage markers (i.e., Ku70), the development of serum biomarkers of CYP17A1, and antigen receptor activity will be crucial to identify those patients likely to respond to ADT and RT as well as new combined modality combinations.⁷³

Another important limitation of our series was that it was not possible to determine the EBRT dose target coverage per lesion. It is possible in EBRT today to perform heterogeneous planning to mimic BT dosimetry. In that scenario, tumoricidal “hot spots” are deliberately located within the tumor while a dose fall-off bath covers the periphery of the lesion. In that way, the dose to the periphery of the tumor or the prostate may be compromised to respect conservative rectal or urethra dose constraints. Investigators have proposed to manipulate urethra doses not to exceed a maximum of 110% of the prescribed dose although this raises concerns about reducing cancer control for tumors that are too close to the urethra^{74–76}. In addition, with the constant physiological movement of the bladder and rectum, the urethra is a vulnerable organ that may easily get into the high-dose irradiation area. Therefore, controlling the exact location of the prostate and the IDN by tracking intraprostatic fiducial markers during IGRT sessions is an obvious method to improve EBRT delivery.

Among all series, there was variability in terms of use of ADT, which may affect the GTV definition. For instance, it is uncertain whether reducing the IDN radiation volume based on neoadjuvant ADT response may expose the patients to target missing and subsequent risk of recurrence. Our review also highlights the heterogeneity in the administration of ADT in most series. Despite the strong level-1 scientific evidence supporting the use of ADT to conventional EBRT in intermediate- and high-risk patients even in the context of conventional dose escalation up to 78 Gy, only 27.8% of the patients in our series received ADT. This underutilization of ADT was recently highlighted by Ong et al⁷⁷ who prospectively evaluated 1,806 PCa patients treated in the population-based Prostate Cancer Outcome Registry Victoria. They reported that one in five men with high-risk PCa and one in two with unfavorable intermediate-risk PCa did not receive ADT with RT. It is possible that in our series, patients have declined standard ADT in the hopes that experimental higher dose radiation to the prostate could provide equal disease control with better QoL and especially sexual QoL compared with the addition of ADT. Based on the current evidence, it is difficult to rule out that dose escalation to the IDN could provide a benefit on local tumor control in the same magnitude than the addition of ADT.

Last but not least, our systematic review revealed relatively few studies with patient-reporting outcomes for assessing toxicity. Future trials should incorporate global health and prostate-specific QoL questionnaires to be able to capture the patient's experience with these new treatments.

Supplementary Table 3 shows prospective registered clinical trials that may provide further evidence to implement this technique in the future^{11,42,46,78–80}.

The most appropriate radiation dose level, dose constraints, the size of margins, lymph node treatment, and whether neoadjuvant or adjuvant ADT provides any benefit are variables yet to be

determined. These caveats should be taken into account before drawing definitive conclusions.

5. Conclusion

Keeping in mind the limitations of this systematic review, there are encouraging results for focal dose escalation to the IDN with acceptable short- to medium-term side effects and biochemical disease control rates. However, owing to the heterogeneity of the studies included, there are many confounding factors limiting the scope of this review. Considering that the clinical endpoint in the studies was biochemical recurrence, the use and duration of ADT administration should be carefully considered before driving definitive conclusions. Randomized trials following similar hypofractionated regimens with sufficient follow-up are needed before this technique can be generally recommended. Therefore, patients who intend to be treated with a dose escalation to the IDN should be enrolled in clinical trials.

Conflicts of interest

None to be declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pnrl.2018.03.005>.

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